Italianity is associated with lower risk of prostate cancer mortality in Switzerland

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Abstract: PURPOSE: Different prostate cancer mortality rates observed in European countries may depend on cultural background. We aimed at exploring variation in prostate cancer mortality in the language regions of Switzerland as a function of "Italianity", a proxy for adherence to an Italian lifestyle. METHODS: We used data of the Swiss National Cohort, a census-based record linkage study, consisting of census (1990 and 2000) and mortality (until 2008) data. 1,163,271 Swiss and Italian nationals 40+-year old were included. Multivariate age-standardized prostate cancer mortality rates and hazard ratios (HR) from Cox proportional hazards regression analysis were performed. Italianity was defined by an individual's nationality, place of birth and principal language, resulting in a score of 0-3 points. RESULTS: Age-standardized prostate cancer mortality rates (per 100,000 person-years) were lowest in the Italian-speaking region of Switzerland (66.7 vs. 87.3 in the German-speaking region). Both Italian nationality and/or place of birth were significantly associated with lower mortality. There was a graded inverse association between mortality rates and increasing Italianity score. Individuals with the highest level of Italianity had a HR of 0.67 (95 % CI 0.59-0.76) compared to those with an Italianity score of zero. Results were similar when looking at language regions separately. CONCLUSIONS: The strong and consistent association between Italianity and prostate cancer mortality suggests protective properties of an Italian lifestyle. Further research is required in order to determine which factors specific for Italian culture are responsible for the lower prostate cancer mortality.

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ORIGINAL PAPER

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Conclusions The strong and consistent association between Italianity and prostate cancer mortality suggests protective properties of an Italian lifestyle. Further research is required in order to determine which factors specific for Italian culture are responsible for the lower prostate cancer mortality.

Keywords Prostate cancer · French · German · Italian · Nationality · Place of birth · Migrants

For the Swiss National Cohort Study Group.

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Introduction

In Europe, prostate cancer is the most frequently diagnosed cancer and the third leading cause of cancer death in men [1]. The age-standardized incidence rate almost doubled from 47 to 93 cases per 100,000 person-years between 1995 and 2008, while mortality decreased from 23.5 to 19.3 between 1995 and 2012 [2, 3].

Prostate cancer develops from dysplastic lesions [4]. It rarely occurs in individuals aged <50 years but is very frequent in men aged >85 when relying on autopsies [5]. However, the probability of dying from prostate cancer in these men is only about 3 % [6]. In Europe, there is a

distinct north–south gradient with higher incidence rates in Sweden, The Netherlands, Germany and lower ones in Italy and Spain [7, 8]. Up to date, familial heredity and race/ethnicity are widely accepted risk factors in addition to older age. To our knowledge, a potential impact of cultural background has not been examined yet.

In Switzerland, prostate cancer is the second leading cause of cancer deaths in men [9]. About 30 % of incident cases and 15 % of cancer deaths are attributable to prostate cancer [10]. The estimated age-standardized mortality rate in 2012 was 21.8 per 100,000 person-years. Interestingly, despite geographical proximity, this rate is substantially higher than in Italy (14.1) [3]. However, variation between countries can be delusive because they are prone to differences in data collection and processing or in assignment of causes of death [3–5]. Furthermore, the differences could be a consequence of divergent national health policies and healthcare systems.

Switzerland is divided into three main language regions (German, French and Italian). The cultural habits in each language region are in many respects similar to those of the neighboring countries Germany, France and Italy. We aimed at investigating cultural variation in prostate cancer mortality in Switzerland. In particular, we examined the impact of the level of "Italianity", defined by an individual's nationality, place of birth and principal language, taking into consideration also the language region of residence. Switzerland offers a unique setting for the investigation of the "pure" impact of cultural environment on mortality because it combines cultural diversity with a common national health and statistical system.

Methods

Data

The Swiss National Cohort is a census-based cohort study, with anonymous record linkage of individual data from census and mortality registry. In 1990 and 2000 all individuals living in Switzerland had to fill out self-administered questionnaires, with a participation rate of at least 98 % [11]. Personal data on sex, age, place of residence, country of birth, nationality, principal language, educational level and marital status from the 1990 census was linked to the 2000 census and to death (including cause of death) and emigration files until 2008 [12]. Mortality registration in Switzerland is virtually complete and coding of causes of death is conducted centrally at the Swiss Federal Statistical Office in Neuchâtel. Prostate cancer deaths were identified by codes 185 (ICD-8, until 1994) or C61 (ICD-10, since 1995) [13].

In this study, we included 1,424,615 men aged ≥40 years on 4 December 1990 (date of census). We restricted the analyses to men reporting any of the four official Swiss languages as principal language ($n = 1{,}333{,}736$) and, additionally, who were born either in Italy or in Switzerland and were of Swiss or Italian nationality ($n = 1{,}201{,}609$). In a further step, 38,338 men of the 1990 census population were excluded because they could neither be linked to a 2000 census record nor were documented to have died or emigrated. Our final dataset consisted of 1,163,271 men.

Local background

Switzerland has four national languages. For our analyses, we differentiated between German, French and Italian-speaking areas, in the following referred as German, French and Italian Switzerland. Romansh, the fourth national language, is only spoken by a small minority and does not cover a contiguous geographical area. Since all Romansh speakers master German, the Romansh municipalities were added to German Switzerland.

Until 1980, censuses included only one language item ("What language do you think in and do you master best?"), permitting only a single response. Since 1990, mastered languages were assessed by two questions ("what language do you think in and do you master best?" and "which language do you speak regularly?"). For our study, we considered the first question to be assigned as reliable for principal language.

In this study, migration background is conceptualized by considering both, citizenship (called "nationality" in the this text) and birthplace. In Swiss law, citizenship is acquired through descent (jus sanguinis) or naturalization (demanding for having lived in the country for several years and for sufficient knowledge of regional language).

Italians were the most numerous foreign population group in Switzerland since World War II, reaching a maximum of 555,000 persons in 1974 (seasonal workers not included)—i.e., 52 % of all foreign nationals or almost 9 % of the overall population of Switzerland at that time [14]. Thus, in Switzerland, there is a substantial number of second and even third generation Italians. For this study, we combined information on nationality and place of birth as follows:

1. Swiss nationality and born in Switzerland (CH, CH)
2. Swiss nationality and born in Italy (CH, IT) or Italian nationality and born in Switzerland (IT, CH)
3. Italian nationality and born in Italy (IT, IT)

These two variables and the additional variable principal language were used to build a score to assess the level of

Italianity for each individual. Each of these variables (principal language, nationality and place of birth) could either be "Italian" or "Non-Italian", resulting in a sum of 0 ("Non-Italian" in each of the variables) to 3 ("Italian" in each of the three variables).

Statistical analyses

Analyses were conducted with STATA version 12.1 (Stata Corporation, College Station, TX, USA), and $p < 0.05$ was considered to be statistically significant (two-sided tests).

Descriptive statistics included means, counts and relative frequencies. Mortality rates were age-standardized using the WHO standard population "Europe" [10] and multivariable Cox regression models were calculated for modeling survival in cohort studies. In these, we included marital status, age, age squared, educational level and a period dummy. The proportional hazard assumption was fulfilled for all variables except marital status, which therefore was excluded from further analyses. Hazard ratios (HR) and corresponding 95 % confidence intervals (CI) were calculated for each language region. The Italianity score was analyzed for German and French Switzerland. Italian Switzerland was excluded from these analyses because the principal language of most men living in this region is Italian and, thus, these men have a higher Italianity score anyway. Furthermore, different weighting models were evaluated for the Italianity score (doubling the values of each of the variables from the score) with the Bayesian Information Criterion (BIC). Sensitivity analyses were conducted using a competing risks model [15] that took into account deaths from all other possible causes.

Furthermore, we separately analyzed data of only the first observation period (1990–2000) to evaluate whether there might be discrepancies due to undetected loss to follow-up in the second period.

Covariates in our analyses included educational level (compulsory education, secondary education, tertiary education, missing or unclear information), marital status (single, married, widowed and divorced), age and age squared (continuous, to model the exponential increase in mortality with age) and principal language (German, French and Italian). Because between 2000 and 2008 an unknown number of men may be lost to follow-up, we modeled the lacking information by introducing a dummy variable for the 2 periods. The first observation period began on 4 December 1990 (date of 1990 census) and ended on 4 December 2000. The second period ranged from 5 December 2000 (date of 2000 census) to 31 December 2008. All individuals without a linked emigration or death record were assumed to be alive at the end of 2008.

Table 1 Baseline characteristics, Swiss National Cohort, 1990–2008, 40+ years at baseline

	Language region		
	German Switzerland	French Switzerland	Italian Switzerland
Men[a]	*n* (%)	*n* (%)	*n* (%)
CH, CH	795,143 (93.1)	223,460 (89.1)	39,693 (67.8)
CH, IT	4,461 (0.5)	2,449 (1.0)	3,956 (6.8)
IT, IT	52,154 (6.1)	23,671 (9.4)	14,012 (23.9)
IT, CH	2,194 (0.3)	1,197 (0.5)	881 (1.5)
Total	853,952 (100)	250,777 (100)	58,542 (100)
Deaths due to prostate cancer[a]			
1990–2008	15,884 (100)	4,502 (100)	802 (100)
CH, CH	15,611 (98.3)	4,313 (95.8)	648 (80.8)
CH, IT	52 (0.3)	40 (0.9)	47 (5.9)
IT, IT	186 (1.2)	122 (2.7)	87 (10.8)
IT, CH	35 (0.2)	27 (0.6)	20 (2.5)
Person-years			
1990–2008	12,307,150	3,584,593	844,749
Mean age, years	57.6	57.8	57.1
	%	%	%
Education			
Missing/unclear information	0.7	0.9	0.7
Compulsory	25.2	34.4	35.5
Secondary	54.3	45.3	49
Tertiary	19.8	19.5	14.8
Principal language			
German (incl. Rhaeto-Romanic)	92.2	7.5	8.4
French	1.4	83.6	1.3
Italian	6.4	8.9	90.3
Marital status			
Single	9.1	9.1	9.7
Married	80.1	78.8	80.8
Widowed	5.1	5.4	4.6
Divorced	5.7	6.7	4.9

Baseline at 4 December 1990

[a] Nationality is set before comma, and place of birth after comma

Results

More than two-thirds of men included in this analysis lived in German Switzerland, whereas only 5 % lived in Italian Switzerland. From this follows a comparably small number of deaths due to prostate cancer in this region. In all three language regions, the mean age at baseline was very similar. The percentage of men with tertiary education was lowest in Italian Switzerland, and secondary education was most prevalent in German Switzerland (Table 1).

Table 2 Age-standardized prostate mortality rates per 100,000 person-years, 1990–2008, men aged 40+ years at baseline

	Language region									
	German Switzerland			French Switzerland			Italian Switzerland			Total
Men[a], *n*	Deaths	Mortality rates	95 % CI	Deaths	Mortality rates	95 % CI	Deaths	Mortality rates	95 % CI	Deaths	Mortality rates	95 % CI
CH, CH	15,611	88.1	86.7–89.5	4,313	83.5	81.0–86.1	648	69.5	63.9–75.0	20,572	86.4	85.2–87.6
CH, IT or IT, CH	87	59.2	46.5–72.0	67	78.1	59.0–97.1	67	63.6	47.9–79.3	221	66.0	57.1–74.9
IT, IT	186	66.8	51.1–82.6	122	53.1	41.4–64.9	87	55.0	42.0–68.1	395	57.6	50.1–65.1
Total	15,884	87.3	85.9–88.7	4,502	82.1	79.6–84.5	802	66.7	62.0–71.4	21,188	85.2	84.0–86.3

Baseline at 4 December 1990

[a] Nationality is set before comma, and place of birth after comma

Principal language of the individual being the same as the predominant language of the region of residence varied from 83.6 to 92.2 % and marital status was distributed similarly among the language regions.

Age-standardized prostate cancer mortality rates (per 100,000 person-years) were lowest in Italian Switzerland (66.7 vs. 87.3 in German Switzerland; Table 2). For Italian-born men with Italian nationality, prostate cancer mortality rate was lowest (57.6) and for Swiss-born men with Swiss nationality highest (86.4). In German and French Switzerland, prostate cancer mortality rates among Italian-born Italians were significantly lower than among Swiss-born men with Swiss nationality.

Italian nationality and/or place of birth were significantly associated with lower mortality in German Switzerland compared to Swiss nationals born in Switzerland (Table 3). After including principal language as an additional covariate, we observed slightly less decreased HR for all non-referent categories. However, the confidence intervals of the estimated HRs in the Italian language region, especially for men with Italian nationality and place of birth, are quite wide due to the small number of individuals and deaths in that particular stratum. Therefore, these estimates are not statistically significant and should be interpreted with caution.

In a further step, mortality in dependence on Italianity level (based on nationality, place of birth and principal language) was analyzed (Fig. 1), with adjustment for observation period, age, age squared, education and language region. Results showed that the Italianity score performed best without weighting of any of the three variables language, nationality or place of birth (data not shown).

Combining German and French Switzerland, we observed a 50 % lower mortality (HR of 0.67, 95 % CI 0.59–0.76) among individuals with the highest Italianity score compared to no-Italianity (Fig. 1). Furthermore, there was a gradual decrease of mortality with increasing Italianity score. Results remained statistically significant when looking at German and French Switzerland separately (HR 0.66, 95 % CI 0.57–0.77 in the German-speaking region and HR 0.67, 95 % CI 0.55–0.81 in the French-speaking region, highest Italianity score vs. no-Italianity). The consideration of competing risks and sensitivity analyses including only the first observation period left the estimates virtually unchanged (data not shown).

Discussion

We examined prostate cancer mortality in the three language regions of Switzerland with a focus on Italianity. Prostate cancer mortality was lowest in Italian Switzerland.

Table 3 Multivariate adjusted Cox regression model, 1990–2008, men aged 40+ years at baseline

Nationality and place of birth[b]	Language region	Model 1[a]		Model 1[a] with additional adjustment for principal language	
		HR	95 % CI	HR	95 % CI
CH, CH	German	1.00	Ref.	1.00	Ref.
CH, IT or IT, CH	German	0.67	[0.58, 0.77]	0.80	[0.66, 0.97]
IT, IT	German	0.68	[0.49, 0.95]	0.69	[0.50, 0.97]
CH, CH	French	0.95	[0.92, 0.99]	0.97	[0.90, 1.05]
CH, IT or IT, CH	French	0.64	[0.54, 0.77]	0.76	[0.61, 0.94]
IT, IT	French	0.74	[0.51, 1.08]	0.77	[0.52, 1.12]
CH, CH	Italian	0.79	[0.73, 0.85]	0.93	[0.81, 1.07]
CH, IT or IT, CH	Italian	0.64	[0.52, 0.79]	0.79	[0.61, 1.01]
IT, IT	Italian	0.92	[0.59, 1.42]	1.11	[0.70, 1.76]

Baseline at 4 December 1990

[a] Adjusted for age, squared age, education level, observation period

[b] Nationality is set before comma and place of birth after comma

Italian-born men with Italian nationality and Italian as principal language had a substantially (HR = 0.67) lower prostate cancer mortality risk compared to Swiss-born men with Swiss nationality and German as principal language. There was a graded inverse association of an Italianity score with prostate cancer mortality.

Mortality in different Swiss regions was already evaluated for other causes of death. For example, a higher CVD mortality in the German-speaking region than in the French-speaking region has been described, which is in line with the gradient between Germany and France [16]. With its cultural diversity, Switzerland may reflect mortality risk disparities between different parts of Europe. Italian nationality and place of birth in Italy are typical for "first generation" migrants. These migrants usually have a lower all-cause mortality despite their generally lower socioeconomic status (SES) [17]. This surprising finding was referenced as "Mediterranean migrants' mortality paradox" [18]. This also holds true for prostate cancer, such that Italian migrants have had lower prostate cancer incidence in the target countries compared to the autochthonous population [19, 20]. However, the relative risk differential in all-cause mortality by Italian migration category [17] was only about one-third of the differences found for prostate cancer mortality in our study.

As the National Institute for Cancer Epidemiology and Registration (NICER) reported, age-standardized prostate cancer incidence was higher in the German-speaking region (135.0; 95 % CI 131.0–139.0) than in the canton of Ticino (103.5; 95 % CI 97.4–110.0) [21]. We cannot exclude regional variation in screening policies. However, more prevalent prostate cancer screening does not appear to result in lower prostate cancer mortality [22].

If low SES indeed had a detrimental impact on prostate cancer survival, this would have induced an underestimation of the effect size of Italianity in our population, because Italians in Switzerland tend to have a lower SES than Swiss nationals. In contrast to SES, it is unlikely that the genetic background plays a decisive role: Differences in genetic prostate cancer risk were reported between African-Americans and Americans of European descent but not within ethnically more homogeneous European populations [23].

Among other lifestyle factors, diet is strongly linked to culture and could also play a role in the development and the progression of prostate cancer. High intake of calcium was associated with increased risk of prostate cancer [5], whereas consumption of foods containing lycopene and selenium may be protective [24]. Individuals with a high Italianity score may have a strong adherence to a Mediterranean diet, which is, among others, rich in vegetables (typically fresh and cooked tomatoes), but relatively poor in dairy products, which are a main source of calcium in European countries. In fact, the food supply of tomatoes, which contain lycopene, is markedly higher in Italy than in Switzerland with 60.5 kg/capita/yr in Italy vs. 25.2 in Switzerland (in 2009), whereas calcium intake, consumed with milk and dairy products, is higher in Switzerland [25].

We hypothesize that the historical background of immigration may play a role concerning acculturation: As mentioned before, Italians have been a numerous foreign population group since World War II [14]. Due to the proximity to Italy and the fact that they received a permit for permanent residence only after several years, they may have intended to return to Italy and, thus, took care to preserve their culture of origin, including traditional lifestyle and food, in Switzerland.

Language is a proxy of culture and degree of acculturation [17, 26, 27]. We observed an attenuation of the association between Italianity and prostate cancer mortality once we included principal language into the model, in

particular in the Italian part of Switzerland, which implies that language carries particular aspects of culture and lifestyle that are not captured by nationality, place of birth and place of residence.

Strengths and limitations

The Swiss National Cohort includes virtually the entire population of Switzerland because it is based on mandatory data collection (census, vital statistics). Due to substantial immigration after World War II, there is a large population with different levels of Italian migration background.

Prostate cancer mortality might be overestimated when prostate cancer was erroneously attributed instead of another cause of death. Due to a peculiar priority rule practiced by the Federal Statistical Office until 1994, prostate cancer was actually over registered by about 12 % [28]. Registration of deaths—but not necessarily of cause of death—of Swiss nationals occurred abroad should be fairly complete. However, for foreign nationals residing in Switzerland, registration of deaths occurring abroad is incomplete. This is most serious for deaths of first generation Italians (4–10 %) [17]. However, this could explain only a small fraction of the prostate mortality advantage among this population group. Furthermore, individuals were included if they could be tracked in both censuses (1990 and 2000) and/or linked to a death or emigration record. Due to the study design, the extent of loss to follow-up in the second period (2000–2008) is unknown, but our sensitivity analyses restricting to data from 1990 to 2000 only essentially confirmed the pattern derived from data covering both periods.

In the Swiss National Cohort, only little information on possible risk factors was available. We included them as potential confounders, e.g., by adjusting for educational level as proxy for SES. However, this captures only one dimension of the complex structure of SES [29]. Nevertheless, because in general there are only a few well-established prostate cancer risk factors, this unlikely impairs the validity of our results.

A further limitation is the lack of age at immigration. Italian migrants who arrived in Switzerland in childhood or early adulthood may have higher prostate cancer mortality than those who migrated as adults, which might be due to differences in diet or lifestyle early in life [30].

Finally, associations of risk factors with prostate cancer mortality should be interpreted with caution, because of the latency of decades between exposure and death.

Conclusions

We found a striking protective effect of Italianity on prostate cancer mortality. This association was consistent over the language regions of Switzerland and depended on the level of Italianity. Subjects with Italian nationality, Italian as principal language and being born in Italy had a lower risk than men who did not fulfill all criteria of Italianity. In light of the accelerated ageing of populations in many countries and considering the health burden of prostate cancer, primary prevention is of upmost interest. Specific lifestyle factors related with Italianity should be a subject of further research.

What is already known on this topic

In developed countries, prostate cancer is the most frequently diagnosed cancer and the third leading cause of cancer death in men. Prostate cancer mortality rates vary between European countries, with higher prostate cancer mortality rates being seen in the Nordic countries and lower ones in Mediterranean countries.

What this study adds

In Switzerland, a country with cultural diversity but uniform health and statistical system, level of Italianity

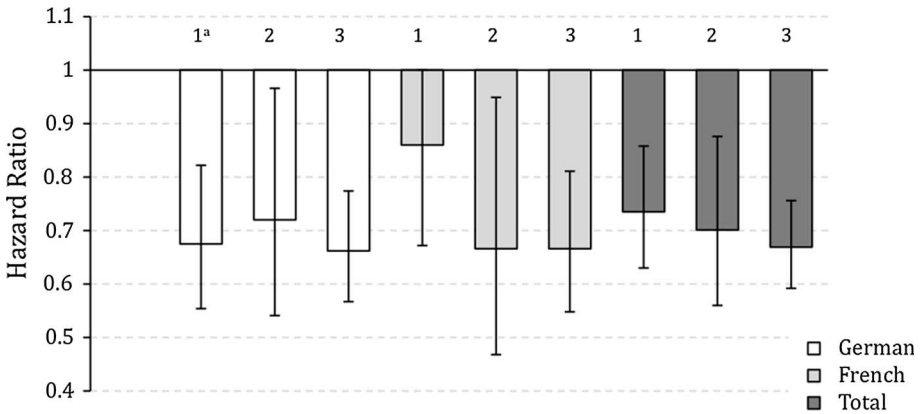

Fig. 1 Hazard ratios of Italianity score (degree of Italianity; 0 points (non-Italian) as reference; max. 3 points for Italian nationality, place of birth and principal language) compared to No-Italianity, for single language regions (adjusted for observation period, age, age squared, education and language region)
[a]Italianity score

(defined by an individual's nationality, place of birth and principal language) was consistently associated with lower prostate cancer mortality. This points to protective lifestyle behaviors inherent to Italian culture, and, thus, searching for factors that potentially contribute to risk reduction in individuals with different level of Italianity may be worthwhile.

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Conflict of interests The authors declare that they have no conflict of interest.

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